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ORIGINAL ARTICLE

Risk factors for atrial fibrillation and their population burden in postmenopausal women: the Women's Health Initiative Observational Study

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ABSTRACT

Objective Atrial fibrillation (AF) is the most common arrhythmia in women. Large studies evaluating key AF risk factors in older women are lacking. We aimed to identify risk factors for AF in postmenopausal women and measure population burden of modifiable risk factors.

Design Prospective observational study.

Setting The Women's Health Initiative (WHI) Observational Study.

Patients 93 676 postmenopausal women were followed for an average of 9.8 years for cardiovascular outcomes. After exclusion of women with prevalent AF or incomplete data, 8252 of the remaining 81 892 women developed incident AF.

Main outcome measures Incident AF was identified by WHI-ascertained hospitalisation records and diagnosis codes from Medicare claims. Multivariate Cox hazard regression analysis identified independent risk factors for incident AF.

Results Age, hypertension, obesity, diabetes, myocardial infarction and heart failure were independently associated with incident AF. Hypertension and overweight status accounted for 28.3% and 12.1%, respectively, of the population attributable risk. Hispanic and African–American participants had lower rates of incident AF (HR 0.58, 95% CI 0.47 to 0.70 and HR 0.59, 95% CI 0.53 to 0.65, respectively) than Caucasians.

Conclusions Caucasian ethnicity, traditional cardiovascular risk factors and peripheral arterial disease were independently associated with higher rates of incident AF in postmenopausal women. Hypertension and overweight status accounted for a large proportion of population attributable risk. Measuring burden of modifiable AF risk factors in older women may help target interventions.

INTRODUCTION

Atrial fibrillation (AF), characterised by chaotic electrical activity in the atrium, remains the most common arrhythmia in adults, affecting over 2.2 million people in the USA,[1] including up to 9.1% of women aged 85 years and older.[2] AF accounts for approximately 75 000 strokes per year[3] and independently increases the risk of death by 1.5–1.9-fold.[4][5] Although AF rates are lower in women than men,[2] women with AF are more likely to develop stroke[3][6][7] and may be at a higher risk of death than men with AF.[4][6]

The aetiology and underlying pathophysiology of AF is poorly understood. Analyses of large prospective cohorts, including the Framingham Heart Study,[8] the Cardiovascular Health Study[9] and others[10][11] have identified the principal independent risk factors of AF including hypertension, diabetes mellitus, obesity, myocardial infarction, coronary heart disease (CHD) and heart failure; these analyses were summarised in a recent systematic review.[12]

Large studies assessing the population-wide, independent contribution of risk factors for incident AF in older women are limited. We therefore conducted this analysis in the multiethnic Women's Health Initiative (WHI) Observational Study (OS) cohort of 93 676 postmenopausal women, one of the largest cohorts available with ascertainment of incident AF.

METHODS

Study population

The WHI-OS is a prospective observational cohort study of postmenopausal women aged between 50 and 79 at baseline, who were recruited at 40 US clinical centres to assess the relationship of various self-reported demographics, such as age, ethnicity, and medical and lifestyle factors on the risk of key health outcomes, such as cardiovascular diseases, including AF, over time. Details of the study design and methods have been previously reported.[13–15] Briefly, participants were recruited, primarily through mass-mailings to age-eligible women, into either a set of clinical trials or the WHI-OS. Excluded were women who were not likely to survive or remain in the vicinity of a given WHI clinic for the next 3 years or who had alcoholism, drug dependency or dementia. A total of 93 676 participants were enrolled between 1994 and 1998.

Study procedure

Women completed baseline self- or interviewer-administered questionnaires for eligibility screening. Baseline characteristics, including demographic, reproductive and personal and family health history, were gathered. Physical examinations,

including clinic height and weight measurements, and blood collections were performed at baseline and again at 3 years. Women were sent questionnaires annually to update their medical and lifestyle information. The study was reviewed and approved by the institutional review boards at each clinical centre, and all participants provided written informed consent.

Definition of baseline variables and end points

Details of study questionnaires, physical measurements, blood collection and quality assurance have been described previously.[13–15] Race and ethnicity were self-reported in the baseline questionnaire, and women who reported a race or ethnicity other than black or Hispanic, such as Asian, Native American, Pacific Islander or other race, were categorised as 'Other'. Baseline AF was self-reported by questionnaire or documented by the presence of AF on a 12-lead ECG during the baseline clinic visit. Peripheral arterial disease (PAD) was ascertained on the baseline questionnaire by asking if the subject had ever been told by her doctor if she had 'claudication or PAD (poor blood flow to the legs or blocked or narrowed arteries to the legs)?'. Baseline questionnaires also assessed for a history of CHD, diabetes, hyperlipidaemia, heart failure and hypertension. In addition, blood pressure measurements at the initial clinic visit identified baseline hypertension, defined as elevated systolic (≥140 mm Hg) or diastolic (≥90 mm Hg) blood pressure. Overweight status was defined as a body mass index (BMI) ≥25 kg/m^2, and obese status was defined as BMI≥30 kg/m^2.

Women were followed with medical history update questionnaires at years 3–8, which specifically probed for hospitalisations. Ascertainment of AF in WHI has been described previously.[16] Medical records were obtained in the event of hospitalisation, and the International Classification of Disease-version 9 (ICD-9) code for AF (427.31) was extracted from these records. WHI data were linked with their Centers for Medicare and Medicaid Services (CMS) data using social security numbers, birth dates and death dates, with 97% of Medicare-eligible WHI participants successfully linked. Among participants with Medicare coverage, incident AF was identified by first occurrence of ICD-9 code 427.31 in any diagnosis position in the inpatient (MEDPAR), outpatient and carrier files during years 1994–2007. Because the Medicare data were available for some participants but not others at different time periods over WHI follow-up, a time-dependent indicator variable of Medicare coverage was added to the Cox hazard models described below to adjust for possible ascertainment bias related to differential exposure to CMS. Medicare time eligible for analysis included those intervals where participants were enrolled in fee-for-service Medicare and not simultaneously enrolled in a Medicare-managed care plan. Women with any single ICD-9 code of 427.31 from review of Medicare claims or hospital records were classified as having new-onset AF.

Statistical analysis

Baseline characteristics of participants with and without incident AF as well as different ethnicities were compared using either the Student t test for continuous variables or the χ^2 test for categorical variables. Assessment of risk factors for incident AF was performed using multivariate Cox hazard regression analysis. For this analysis, the 4397 participants with prevalent AF and 7833 participants with incomplete data were excluded. Multivariate analyses were performed using a primary model containing covariates with known or suspected association with AF including age, race/ethnicity, hypertension, diabetes, hyperlipidaemia, heart failure, myocardial infarction, coronary artery disease, PAD, BMI, smoking, alcohol use, hormone therapy use and level of education. A secondary multivariate model was created with a combined 'atherosclerotic burden' variable defined as PAD, stroke, prior myocardial infarction, coronary bypass surgery or percutaneous coronary angioplasty, and adjusted for all remaining factors from the primary multivariate model.

Associations were reported as HRs with 95% CIs. The proportional hazards assumption was verified by testing the interaction of time and postmenopausal hormone therapy and through visual inspection of the log-likelihood plot of developing AF over time. Kaplan–Meier plots were drawn to depict the relationships between PAD or race/ethnicity and incident AF. The population attributable risk (PAR) of each preventable or treatable risk factor was calculated as the difference between the rate of AF in the entire cohort minus the rate of AF in those who carried the risk factor, divided by the rate of AF in the entire cohort. Analyses were performed using SAS statistical software V.9.1.

RESULTS

Baseline characteristics

Of the 93 676 women enrolled in the OS, 4397 (4.7%) women were excluded because of self-reported baseline AF and 7833 (8.4%) were excluded for missing data, leaving 81 892 women available for analysis. Baseline characteristics of the study group, total and by self-reported race/ethnicity, are presented in table 1, as are statistics for unadjusted differences among ethnic groups. On average, participants were 63 years of age, 42.4% had a history of hypertension, 2.0% reported PAD, 3.9% were self-reported diabetic, and 0.6% had a history of heart failure. Rates of AF increase significantly with age and are higher for women with CHD in all age groups (see online supplementary figure S1). The rate of incident AF in women between 75 and 80 years of age was ~2.8%/year in the absence of CHD, and 4.9%/year in women with CHD.

Risk factors for incident AF

Over an average of 9.8 years, 8252 participants developed new-onset AF with an average annual incidence of 1.02%, including 2021 cases identified only through WHI hospitalisation chart reviews, 4009 cases identified only through CMS coding, and 2222 identified by both methods.

Multivariate-adjusted Cox hazard regression analysis confirmed previous reports that socioeconomic factors, myocardial infarction and multiple cardiovascular risk factors, such as hypertension and diabetes, are independently associated with incident AF (table 2). Heart failure was the strongest independent predictor of incident AF, with a more than twofold higher HR. Current and past tobacco use remained independently associated with incident AF, whereas hyperlipidaemia was not associated with AF after adjustment for other risk factors. Past but not current alcohol use was associated with incident AF. We also found that PAD was predictive of incident AF with a HR of 1.53, independent of CHD, hypertension or the other major cardiovascular risk factors (table 2). Each subgroup with baseline PAD studied, including participants with hypertension and CHD, demonstrated an increased risk of developing AF (see online supplementary figure S2). A Kaplan–Meier plot comparing the cumulative hazard of AF in participants with and without PAD shows a significant separation of the curves (log-rank p<0.001) (figure 1A). In a sensitivity analysis, atherosclerotic burden, defined as presence of PAD, prior myocardial infarction, coronary bypass surgery or percutaneous coronary

Table 1 Baseline characteristics by race/ethnicity, excluding women with baseline atrial fibrillation

Characteristic	All participants (n=81892)	Caucasian (n=74321)	Black (n=7234)	Hispanic (n=3492)	Other (n=4232)	p Value
Demographics						
Age, mean (SD)	63.4 (7.3)	63.7 (7.3)	61.9 (7.3)	60.4 (7.1)	63.6 (7.6)	<0.001
BMI (kg/m^2), mean (SD)	27.2 (5.8)	26.9 (5.7)	30.6 (6.7)	28.4 (5.9)	25.6 (5.3)	<0.001
<25	33 637 (41.1)	29 513 (42.9)	1210 (19.2)	870 (29.7)	2044 (53.1)	
25–<30	27 973 (34.2)	23 465 (34.1)	2181 (34.6)	1122 (38.3)	1205 (31.3)	
30–<35	12 726 (15.5)	10 183 (14.8)	1549 (24.6)	603 (20.6)	391 (10.2)	
35–<40	4748 (5.8)	3613 (5.3)	779 (12.4)	227 (7.8)	129 (3.4)	
≥40	2808 (3.4)	2045 (3.0)	576 (9.2)	106 (3.6)	81 (2.1)	
Income						<0.001
<US$20 000	11 550 (14.1)	8324 (12.1)	1726 (27.4)	890 (30.4)	610 (15.8)	
US$20 000–49 999	33 060 (40.4)	28 126 (40.9)	2418 (38.4)	1090 (37.2)	1426 (37.0)	
US$50 000–74 999	15 625 (19.1)	13 487 (19.6)	1022 (16.2)	359 (12.3)	757 (19.7)	
≥US$75 000	15 944 (19.5)	14 270 (20.7)	635 (10.1)	275 (9.4)	764 (19.8)	
Education						<0.001
≤High school/GED	17 089 (20.9)	13 379 (19.4)	1634 (26.0)	1157 (39.5)	919 (23.9)	
Some college	29 820 (36.4)	25 032 (36.4)	2329 (37.0)	1083 (37.0)	1376 (35.7)	
College degree or higher	34 983 (42.7)	30 408 (44.2)	2332 (37.0)	688 (23.5)	1555 (40.4)	
Medical history						
Hypertension						<0.001
Never treated	47 207 (57.6)	41 089 (59.7)	2250 (35.7)	1814 (62.0)	2054 (53.4)	
Currently untreated	14 475 (17.7)	12 001 (17.4)	1167 (18.5)	525 (17.9)	782 (20.3)	
Treated	20 210 (24.7)	15 729 (22.9)	2878 (45.7)	589 (20.1)	1014 (26.3)	
Diabetes mellitus	3197 (3.9)	1999 (2.9)	764 (12.1)	217 (7.4)	217 (5.6)	<0.001
Hyperlipidaemia	11 909 (14.5)	9647 (14.0)	1047 (16.6)	484 (16.5)	731 (19.0)	<0.001
Statin use at baseline	6616 (8.1)	5483 (8.0)	545 (8.7)	205 (7.0)	383 (9.9)	<0.001
CHD (MI/CABG/PTCA)	2450 (3.0)	1996 (2.9)	278 (4.4)	62 (2.1)	114 (3.0)	<0.001
MI	1678 (2.0)	1349 (2.0)	219 (3.5)	39 (1.3)	71 (1.8)	<0.001
CABG/PTCA	1437 (1.8)	1211 (1.8)	124 (2.0)	33 (1.1)	69 (1.8)	<0.001
CVD (CHD/stroke)	3353 (4.1)	2654 (3.9)	426 (6.8)	110 (3.8)	163 (4.2)	<0.001
Stroke	1069 (1.3)	780 (1.1)	177 (2.8)	55 (1.9)	57 (1.5)	<0.001
Heart failure	514 (0.6)	375 (0.5)	96 (1.5)	21 (0.7)	22 (0.6)	<0.001
Peripheral arterial disease	1600 (2.0)	1253 (1.8)	209 (3.3)	71 (2.4)	67 (1.7)	< 0.001
Deep vein thrombosis	2877 (3.5)	2533 (3.7)	195 (3.1)	63 (2.2)	86 (2.2)	<0.001
Aspirin use at baseline	16 995 (20.8)	15 239 (22.1)	874 (13.9)	329 (11.2)	553 (14.4)	<0.001
Warfarin use at baseline	444 (0.5)	381 (0.6)	40 (0.6)	10 (0.3)	13 (0.3)	0.126
Systolic BP, mean (SD)	126.7 (17.9)	126.2 (17.7)	132.1 (18.4)	125.1 (17.1)	129.2 (18.9)	<0.001
Diastolic BP, mean (SD)	74.8 (9.3)	74.3 (9.2)	78.0 (9.8)	74.6 (9.2)	76.9 (9.7)	<0.001
Heart rate, mean (SD)	69.3 (12.0)	69.3 (12.0)	70.5 (13.0)	68.7 (10.5)	68.5 (11.3)	<0.001
Habits						
Smoking						<0.001
Never	41 619 (50.8)	34044 (49.5)	3156 (50.1)	1842 (62.9)	2577 (66.9)	
Past	35 194 (43.0)	30747 (44.7)	2464 (39.1)	890 (30.4)	1093 (28.4)	
Current	5079 (6.2)	4028 (5.9)	675 (10.7)	196 (6.7)	180 (4.7)	
Alcohol						<0.001
Never	9044 (11.0)	6097 (8.9)	1174 (18.6)	563 (19.2)	1210 (31.4)	
Past	15 066 (18.4)	11 452 (16.6)	2104 (33.4)	700 (23.9)	810 (21.0)	
Current	57 782 (70.6)	51 270 (74.5)	3017 (47.9)	1665 (56.9)	1830 (47.5)	

All values represent the total (percentage) unless otherwise indicated.
BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; CHD, coronary heart disease; CVD, cardiovascular disease; GED, general educational development; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

angioplasty, was predictive of AF with a HR of 1.63 (95% CI 1.51 to 1.75). The PAR estimates of the most significant reversible or treatable risk factors from the multivariate model are presented in table 3. The risk factor that contributed most to the population-wide risk of incident AF was hypertension (PAR=28.3%), followed by overweight or obese status (PAR=12.1%) (table 3).

Ethnicity/race and AF
After exclusion of baseline AF, the WHI-OS cohort consisted of 7234 (8.8%) African-American women, 3492 (4.3%) Hispanic women, 421 (0.45%) Asian/Pacific Islanders and 2671 (2.8%) American-Indian women (Table 1). After adjustment for age, socioeconomic status and other cardiovascular risk factors, African–American women, Hispanic women and women of

Table 2 Univariate and multivariate-adjusted HRs of incident atrial fibrillation for several demographic and clinical factors

Characteristic	Unadjusted		Age/ethnicity adjusted		Multivariate adjusted	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Age (5 year increase)	1.54 (1.51 to 1.56)	<0.001	1.53 (1.50 to 1.56)	<0.001	1.49 (1.47 to 1.52)	<0.001
Race/ethnicity		<0.001		<0.001		<0.001
White	1.00		1.00		1.00	
African–American	0.68 (0.61 to 0.76)		0.76 (0.69 to 0.85)		0.59 (0.53 to 0.65)	
Hispanic	0.50 (0.41 to 0.61)		0.60 (0.49 to 0.73)		0.58 (0.47 to 0.70)	
Other	0.67 (0.59 to 0.77)		0.66 (0.58 to 0.76)		0.67 (0.59 to 0.77)	
PAD	2.37 (2.12 to 2.64)	<0.001	2.06 (1.85 to 2.30)	<0.001	1.53 (1.37 to 1.72)	<0.001
Hypertension	1.83 (1.76 to 1.92)	<0.001	1.59 (1.52 to 1.67)	<0.001	1.43 (1.36 to 1.50)	<0.001
Diabetes	2.08 (1.91 to 2.27)	<0.001	2.13 (1.95 to 2.33)	<0.001	1.55 (1.42 to 1.70)	<0.001
Hyperlipidaemia	1.28 (1.21 to 1.35)	<0.001	1.16 (1.10 to 1.23)	<0.001	0.95 (0.89 to 1.00)	0.069
Heart failure	4.02 (3.42 to 4.73)	<0.001	3.65 (3.10 to 4.29)	<0.001	2.19 (1.85 to 2.60)	<0.001
Coronary heart disease	2.84 (2.61 to 3.09)	<0.001	2.30 (2.12 to 2.51)	<0.001	1.76 (1.61 to 1.93)	<0.001
BMI (5 kg/m^2 increase)	1.13 (1.11 to 1.15)	<0.001	1.18 (1.16 to 1.20)	<0.001	1.12 (1.10 to 1.14)	<0.001
PHT use ever	0.87 (0.83 to 0.91)	<0.001	0.99 (0.94 to 1.03)	0.510	1.03 (0.98 to 1.07)	0.285
Smoking		<0.001		<0.001		<0.001
Never	1.00		1.00		1.00	
Past	1.15 (1.10 to 1.20)		1.20 (1.15 to 1.25)		1.18 (1.13 to 1.24)	
Current	1.08 (0.98 to 1.20)		1.31 (1.18 to 1.44)		1.32 (1.19 to 1.46)	
Alcohol use		<0.001		<0.001		0.006
Non-drinker	1.00		1.00		1.00	
Past	1.17 (1.08 to 1.27)		1.22 (1.12 to 1.32)		1.09 (1.00 to 1.18)	
Current	0.94 (0.88 to 1.01)		0.98 (0.92 to 1.06)		1.00 (0.93 to 1.07)	
Education		<0.001		<0.001		0.004
≤High school/GED	1.00		1.00		1.00	
Some college	0.89 (0.84 to 0.94)		0.91 (0.86 to 0.96)		0.94 (0.88 to 0.99)	
College degree or higher	0.76 (0.71 to 0.80)		0.81 (0.77 to 0.86)		0.91 (0.86 to 0.96)	

All demographic and clinical characteristics listed in the first column were included in the multivariate model.
BMI, body mass index; GED, general educational development; HR, Cox HR; PAD, peripheral arterial disease; PHT, postmenopausal hormone therapy.

other ethnicities were less likely to develop AF when compared with Caucasians (table 2). A Kaplan–Meier plot comparing the cumulative hazard of AF in participants of different ethnicities shows a significant separation of the curves (log-rank p<0.001) (figure 1B).

DISCUSSION

In this large multiethnic, postmenopausal cohort, women developed AF at an average rate of 1.02% per year, with age-matched rates that were comparable to those reported in prior studies that used Medicare data for AF ascertainment.[12] [17] Risk factors that have been established in other large cohort studies,[8–12] including hypertension, CHD, diabetes and heart failure, were also associated with AF in the WHI cohort. Hypertension and obesity, important modifiable risk factors, contributed significantly to the population risk. In addition, independent of these well-established risk factors, PAD and ethnicity were associated with incident AF. Although others have reported a correlation between PAD and prevalent AF[18] [19] or subclinical atherosclerosis and incident AF, none of the previous large cohort studies[8–11] evaluated the independent relationship between PAD and incident AF.

Higher BMI was significantly associated with incident AF independent of diabetes mellitus, coronary disease or other major cardiovascular risk factors, with a 17% increased risk for every 5 kg/m^2. Obesity has been previously described as an important risk factor for AF,[20] [21] and the effects may be mediated through increased left atrial size[20] or presence of pericardial fat.[22] Studies from the Framingham[8] and Atherosclerosis

Risk in Communities (ARIC)[23] cohorts are the only other large population-based studies that have reported the burden of disease attributed to modifiable risk factors. We report that, in older women, overweight status or obesity accounted for an alarmingly high PAR (12.1%), second only to hypertension. Similarly, in the ARIC cohort, obesity accounted for 12.7% of the PAR.[23] Given the obesity epidemic, this is yet another reason more attention should be paid to population-based efforts to control obesity and to further study the mechanisms linking obesity and AF.

Although the links between PAD and coronary or cerebral vascular disease are well established, it is less clear why PAD is independently associated with AF. PAD was determined by self-report at baseline and therefore may represent a subset of women with a heavier burden of atherosclerotic disease. Further studies are needed to examine the role of PAD in modulating the risk of AF itself.

We and other population studies[2] [9] [24] have found that rates of incident AF are lower in African–Americans than Caucasians, suggesting possible underlying environmental or genetic risk factors related to race. Previous studies in veteran male populations where different race groups had similar access to healthcare reported similar findings.[25] [26] These differences persist despite adjustment for socioeconomic factors. In admixture studies of African–Americans, European ancestry is associated with AF in cohorts containing men and women.[27] Further studies will be necessary to better determine how much of the difference in rates of AF is accounted for by genomic ancestry versus differential environmental exposures.

Figure 1 (A) Cumulative hazard of atrial fibrillation (AF) by baseline peripheral arterial disease (PAD) status. (B) Cumulative hazard of AF by ethnicity. Access the article online to view this figure in colour.
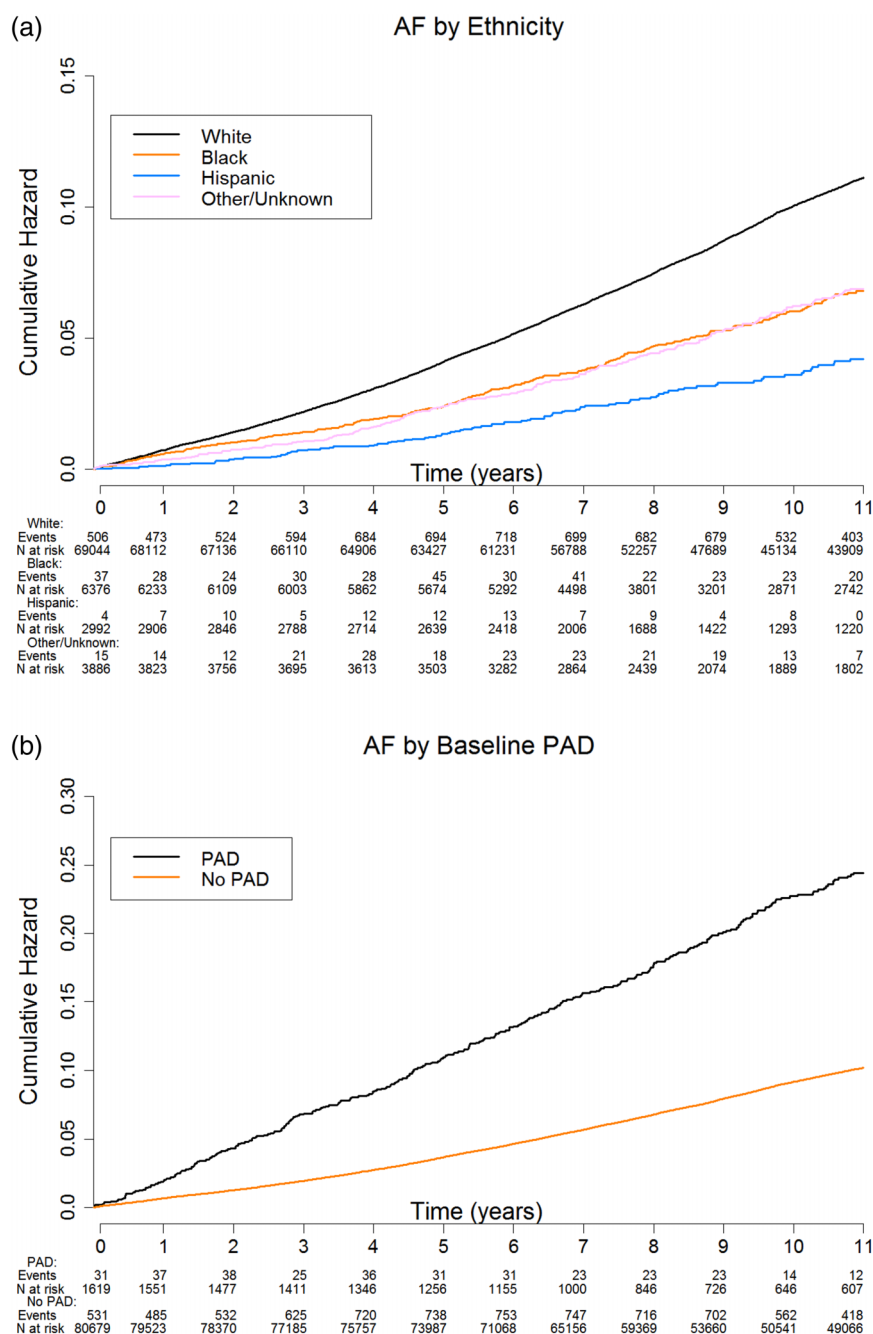

(a) AF by Ethnicity

(b) AF by Baseline PAD

Table 3 Population attributable risk (PAR) of reversible or treatable risk factors of atrial fibrillation

Characteristic	PAR%
Hypertension	28.3
Overweight or obese	12.1
Diabetes mellitus	3.4
Past smoking	5.9
Past alcohol use	3.8
Peripheral arterial disease	2.5
Heart failure	1.4
Coronary heart disease	4.7
No college education	4.4

PAR%, [(total rate−unaffected annualised rate)/(total rate)]×100.
Overweight or obese, body mass index ≥25.

We have previously reported details of the methods used to link WHI participants to their Medicare claims records and ascertain incident AF.[16] Approximately 98% of incident cases identified by WHI ECG or ICD-9 coding from hospitalisation in women enrolled in Medicare at the time were identified through CMS linkage. ICD-9 codes for identification of AF have been used by several large population-based cohorts.[2 9 24] The use of ICD-9 coding to correctly identify incident AF has been validated in several large population-based cohorts,[2 9 24] with a median positive predictive value of 89%,[24 28–31] as detailed further in a recent systematic review.[32] Our previous sensitivity analyses using stricter definitions of incident AF did not significantly change our findings.[16] We found that HR estimates using Medicare ascertainment alone were similar to those found using WHI ascertainment (data not shown). Nevertheless, AF can be asymptomatic and paroxysmal, making

the diagnosis difficult in a subgroup of women. Although there is a potential for misclassification regardless of the definition used, the biases introduced would generally be non-differential, probably resulting in dilution of associations towards the null.

In summary, we found that PAD was a significant risk factor for incident AF in postmenopausal women, independent of other cardiovascular diseases and risk factors, and that hypertension and obesity together accounted for over one-third of the PAR for AF. We also report that, compared with Caucasian women, African–American and Hispanic women are protected from developing AF, independent of socioeconomic and cardiovascular risk factors. Further studies that explore the link between vascular disease, obesity and AF are warranted.

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REFERENCES
1   Feinberg WM, Blackshear JL, Laupacis A, et al. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med* 1995;155:469–73.
2   Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001;285:2370–5.
3   Wolf PA, Mitchell JB, Baker CS, et al. Impact of atrial fibrillation on mortality, stroke, and medical costs. *Arch Intern Med* 1998;158:229–34.
4   Benjamin EJ, Wolf PA, D'Agostino RB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998;98:946–52.
5   Conen D, Chae CU, Glynn RJ, et al. Risk of death and cardiovascular events in initially healthy women with new-onset atrial fibrillation. *JAMA* 2011;305:2080–7.
6   Friberg J, Scharling H, Gadsboll N, et al. Comparison of the impact of atrial fibrillation on the risk of stroke and cardiovascular death in women versus men (The Copenhagen City Heart Study). *Am J Cardiol* 2004;94:889–94.
7   Avgil Tsadok M, Jackevicius CA, Rahme E, et al. Sex differences in stroke risk among older patients with recently diagnosed atrial fibrillation. *JAMA* 2012;307:1952–8.
8   Benjamin EJ, Levy D, Vaziri SM, et al. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA* 1994;271:840–4.
9   Psaty BM, Manolio TA, Kuller LH, et al. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation* 1997;96:2455–61.
10 Stewart S, Hart CL, Hole DJ, et al. Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study. *Heart* 2001;86:516–21.
11 Krahn AD, Manfreda J, Tate RB, et al. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. *Am J Med* 1995;98:476–84.
12 Ball J, Carrington MJ, McMurray JJ, et al. Atrial fibrillation: Profile and burden of an evolving epidemic in the 21st century. *Int J Cardiol* 2013.
13 Anderson G, Cummings S, Freedman LS, et al. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. *Control Clin Trials* 1998;19:61–109.
14 Langer RD, White E, Lewis CE, et al. The Women's Health Initiative Observational Study: baseline characteristics of participants and reliability of baseline measures. *Ann Epidemiol* 2003;13(9 Suppl):S107–21.
15 Curb JD, McTiernan A, Heckbert SR, et al. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. *Ann Epidemiol* 2003;13(9 Suppl):S122–8.
16 Perez MV, Wang PJ, Larson JC, et al. Effects of postmenopausal hormone therapy on incident atrial fibrillation: the women's health initiative randomized controlled trials. *Circ Arrhythm Electrophysiol* 2012;5:1108–16.
17 Piccini JP, Hammill BG, Sinner MF, et al. Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993–2007. *Circ Cardiovasc Qual Outcomes* 2012;5:85–93.
18 Goto S, Bhatt DL, Rother J, et al. Prevalence, clinical profile, and cardiovascular outcomes of atrial fibrillation patients with atherothrombosis. *Am Heart J* 2008;156:855–63, 63 e2.
19 Conway DS, Lip GY. Comparison of outcomes of patients with symptomatic peripheral artery disease with and without atrial fibrillation (the West Birmingham Atrial Fibrillation Project). *Am J Cardiol* 2004;93:1422–5, A10.
20 Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new-onset atrial fibrillation. *JAMA* 2004;292:2471–7.
21 Gami AS, Hodge DO, Herges RM, et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. *J Am Coll Cardiol* 2007;49:565–71.
22 Thanassoulis G, Massaro JM, O'Donnell CJ, et al. Pericardial fat is associated with prevalent atrial fibrillation: the Framingham Heart Study. *Circ Arrhythm Electrophysiol* 2010;3:345–50.
23 Huxley RR, Lopez FL, Folsom AR, et al. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation* 2011;123:1501–8.
24 Alonso A, Agarwal SK, Soliman EZ, et al. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J* 2009;158:111–17.
25 Borzecki AM, Bridgers DK, Liebschutz JM, et al. Racial differences in the prevalence of atrial fibrillation among males. *J Natl Med Assoc* 2008;100:237–45.
26 Perez MV, Yaw TS, Myers J, et al. Prognostic value of the computerized ECG in Hispanics. *Clin Cardiol* 2007;30:189–94.
27 Marcus GM, Alonso A, Peralta CA, et al. European ancestry as a risk factor for atrial fibrillation in African Americans. *Circulation* 2011;122:2009–15.
28 Brass LM, Krumholz HM, Scinto JM, et al. Warfarin use among patients with atrial fibrillation. *Stroke* 1997;28:2382–9.
29 Shen AY, Yao JF, Brar SS, et al. Racial/ethnic differences in ischemic stroke rates and the efficacy of warfarin among patients with atrial fibrillation. *Stroke* 2008;39:2736–43.
30 Shireman TI, Howard PA, Kresowik TF, et al. Combined anticoagulant-antiplatelet use and major bleeding events in elderly atrial fibrillation patients. *Stroke* 2004;35:2362–7.
31 Whittle J, Wickenheiser L, Venditti LN. Is warfarin underused in the treatment of elderly persons with atrial fibrillation? *Arch Intern Med* 1997;157:441–5.
32 Jensen PN, Johnson K, Floyd J, et al. A systematic review of validated methods for identifying atrial fibrillation using administrative data. *Pharmacoepidemiol Drug Saf* 2012;21(Suppl 1):141–7.

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